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Efficacy of Stem Cell Therapy for Tendon Disorders

A Systematic Review

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Investigation performed at Maastricht University, Maastricht, the Netherlands

Background: Stem cell therapy is an emerging treatment for tendon disorders.

Purpose: To systematically review the efficacy of stem cell therapy for patients with tendon disorders.

Study Design: Systematic review; Level of evidence, 4.

Methods: MEDLINE/PubMed, EMBASE, CINAHL, CENTRAL, PEDro, and SPORTDiscus; trial registers; and gray literature were searched to identify randomized controlled trials (RCTs) and non-RCTs, cohort studies, and case series with 5 or more cases. Studies investigating any type of stem cell therapy for patients with tendon disorders were eligible if they included patient-reported outcome measures or assessed tendon healing. Risk of bias was assessed through use of the Cochrane risk of bias tools.

Results: This review included 8 trials (289 patients). All trials had moderate to high risk of bias (level 3 or 4 evidence). In Achilles tendon disorders, 1 trial found that allogenic-derived stem cells led to a faster recovery compared with platelet-rich plasma. Another study found no retears after bone marrow-derived stem cell therapy was used in addition to surgical treatment. There were 4 trials that studied the efficacy of bone marrow-derived stem cell therapy for rotator cuff tears. The controlled trials reported superior patient-reported outcomes and better tendon healing. A further 2 case series found that stem cell therapy improved patient-reported outcomes in patients with patellar tendinopathy and elbow tendinopathy.

Conclusion: Level 3 evidence is available to support the efficacy of stem cell therapy for tendon disorders. The findings of available studies are at considerable risk of bias, and evidence-based recommendations for the use of stem cell therapy for tendon disorders in clinical practice cannot be made at this time. Stem cell injections should not be used in clinical practice given the lack of knowledge about potentially serious adverse effects.

Keywords: tendinopathy; tear; injection; Achilles; shoulder

Tendon disorders are common in athletes and include tendinopathy and partial or complete tendon tears.⁴ Tendinopathy is characterized by pain, swelling, and impaired performance.^{1,26} In some sport disciplines, such as volleyball, more than 50% of athletes develop tendinopathy during their athletic career.²³ The Achilles tendon is the most commonly affected tendon in runners, and approximately 30% of runners will develop Achilles tendinopathy at some point.^{1,26} Tendon tears represent more severe injuries than tendinopathy, and outcomes of tendon tears are often poorer, particularly for rotator cuff tears of the shoulder.²⁰

Various treatment modalities for tendon disorders have been described, such as exercise therapy,^{12,29} shockwave therapy, nonsteroidal anti-inflammatory drugs, and

injection therapy with, for example, corticosteroids, sclerosing substances (aethoxysclerol),³¹ and autologous blood products.¹ Surgery may be required in patients with persistent tendon symptoms or young patients with severe tendon tears.⁹ Despite the abundance of available treatment modalities, outcomes of tendon disorder treatments are often not satisfactory.⁵

Over the past decade, several studies have shown promising results of stem cell therapy in individuals with tendon disorders.^{3,37} Nevertheless, a systematic review performed by our research group in 2017 concluded that there was no evidence for use of stem cell therapy in tendon disorders.³³ Given the increasing use of stem cell therapy in clinical practice, the absence of evidence for or against the use of stem cell therapy in 2017, and new studies having become available on the topic in the past 2 years, an update of our study was warranted.^{17,18,41,48} Therefore, the main purpose of the current systematic review was to reevaluate the efficacy of stem cell therapy based on patient-reported outcome

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measures (PROMs) and tendon healing in individuals with tendon disorders.

METHODS

Protocol Registration and Reporting

This study was registered on PROSPERO (CRD42019116828) on January 10, 2019, before any synthesis was commenced. The PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines were followed for planning, conducting, and reporting this study.²⁸

Research Question and Inclusion and Exclusion Criteria

The research question was to assess the efficacy of stem cell therapy (any type) on PROMs and tendon healing in patients with tendon disorders (any type). Our primary outcomes were PROMs, and our secondary outcome measures were tendon healing measured with magnetic resonance imaging (MRI) or ultrasonography. The inclusion and exclusion criteria are summarized in Table 1.

Search Strategy

A sensitive search strategy was used as previously described.³³ This strategy was based on indexed and free text terms and composed in collaboration with a research librarian (see Appendix 1, available as supplemental material). The electronic databases MEDLINE/PubMed, CENTRAL, EMBASE, CINAHL, PEDro, and SPORTDiscus were searched from inception to November 2018 by 2 independent authors (N.A.C.v.d.B. and M.H.M.). We did not apply any restrictions to our search strategy. Reference lists of included studies were scanned to identify any additional relevant reports. In addition, we searched for ongoing trials in several national (<http://www.trialregister.nl>) and international (<http://www.controlled-trials.com>) trial registries, the WHO trial register (apps.who.int/trialsearch), the EU clinical trial register (<http://www.clinicaltrialsregister.eu>), and ClinicalTrials.gov. We attempted to contact primary investigators to collect additional information about trials identified through these sources. Last, we searched for unpublished studies in OpenGrey (<http://www.opengrey.eu>), the British Library Inside (http://explore.bl.uk/primo_library/libweb/action/search.do?vid=BLVU1), Web of Science, and BIOSIS

TABLE 1
Inclusion and Exclusion Criteria^a

Inclusion criteria

- Published or unpublished studies; randomized or nonrandomized trials and case series with ≥ 5 cases
- Individuals diagnosed with a tendon disorder based on physical examination or imaging (eg, MRI, ultrasonography)
- Study reported at least 1 of the following:
 - ♦ Patient-reported outcomes such as functional scales (eg, VISA-A), pain scales, time to recovery (or return to play), and/or recurrences
 - ♦ Tendon healing as measured with MRI or ultrasonography
- Stem cells of any origin (bone marrow, adipose tissue, etc) used as a treatment
- For controlled trials, the comparison of efficacy of stem cell therapy with another treatment modality or no intervention

Exclusion criteria

- Trials that included patients with tendinopathy who had other concurrent injury

^aThese criteria were similar to the criteria previously used by Pas et al.³³ We reported recurrent tendon disorders, as measured with patient-reported outcomes, as an additional outcome measurement. MRI, magnetic resonance imaging; VISA-A, Victorian Institute of Sport Assessment–Achilles questionnaire.

previews (<http://www.ovid.com>). Authors of potentially eligible studies were contacted for additional information on their studies.

Study Selection

After removal of duplicates, 2 authors (N.A.C.v.d.B. and M.H.M.) independently screened titles and abstracts for potential eligible studies. Subsequently, both authors independently appraised full-text content and applied our inclusion and exclusion criteria. Discrepancies in inclusion of articles were resolved by a third reviewer (M.W.).

Data Extraction

A standardized data extraction sheet was adopted from the Cochrane Collaboration Centre and modified for the purpose of our study.⁴³ Data extraction was performed by 2 authors (N.A.C.v.d.B. and M.H.M.) independently, including study design, year of publication, duration of follow-up, study population characteristics (eg, mean age, sex

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distribution), tendon injury type and location, stem cell type, injection frequency, primary and secondary outcome measurements, and main results of the studies. Disagreements were resolved by a third reviewer (M.W.).

Risk of Bias Assessments

Risk of bias was assessed independently by 2 authors (N.A.C.v.d.B., M.H.M.) for each outcome in each study. The Cochrane Risk of Bias (RoB 2) tool was used to assess the 5 major domains of biases.⁴² This tool provides an algorithm to reach an overall risk of bias judgment per study outcome. The 2 authors independently assessed bias (1) arising from the randomization procedure, (2) due to deviations from the intended interventions, (3) due to missing outcome data, (4) in measurement of the outcome, and (5) in selection of the reported result to make an overall risk of bias judgment for each study outcome. Each domain was completed after the signaling questions as proposed by the guidance of the RoB 2 tool.

Each separate domain was labeled as “low risk of bias,” “some concerns,” or “high risk of bias.” Outcomes of randomized controlled trials (RCTs) were considered to have low risk of bias for the overall judgment when all 5 domains of bias were scored “low risk of bias.” RCT outcomes were considered to entail some concerns for the overall risk of bias if at least 1 of the 5 domains was judged as having “some concerns” about bias. RCT outcomes were considered to have high risk of bias for the overall judgment if at least 1 of the 5 domains of bias was scored as “high risk of bias.” In case of disagreement between the 2 authors, a third reviewer (M.W.) made the final decision.

The Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) was used to assess risk of bias in non-RCTs, and the Newcastle Ottawa Scale was used to assess the quality of case series. Using the Newcastle Ottawa Scale, a maximum of 6 stars could be awarded. Six stars indicated perfect quality, whereas 0 stars indicated very low quality. Appendices 2 through 5 provide details.

Data Synthesis

Data synthesis was planned for RCTs if at least 2 studies investigated the same treatment comparison and studies were clinically homogeneous (ie, identical stem cell type and tendon disorder, cointerventions, mode of injection or transplant). The mean difference expressed the comparative efficacy if studies used the same outcome measure. Standardized mean differences expressed comparative efficacy for studies that used different measures to estimate treatment effects. *P* values less than .05 were considered significant for all analyses. Fixed-effects models were planned to pool data that were statistically homogeneous or when fewer than 3 studies were available for data synthesis. We used random effects models if statistical heterogeneity was present and when 3 or more studies were available. If heterogeneity was present and a sufficient number of studies were available ($n \geq 10$), we planned a subgroup analysis or meta-regression analysis to explore potential sources for heterogeneity (age and sex).

TABLE 2
Oxford Centre for Evidence-Based Medicine 2011
Levels of Evidence for Interventions^a

Level 1	Systematic reviews
Level 2	Randomized controlled trials with low/moderate risk of bias or observational studies with dramatic effect
Level 3	Non-randomized controlled trials with low/moderate risk of bias or randomized controlled trials at high risk of bias
Level 4	Case series, case-control studies, historically controlled studies, or non-randomized controlled trials at high risk of bias
Level 5	Mechanism-based reasoning/expert opinion

^aFrom Oxford Centre for Evidence-Based Medicine.⁴⁴

Descriptive synthesis was performed when data pooling was not possible.

Levels of Evidence

Levels of evidence were assigned to further specify the strength of the studies as proposed by the Oxford Centre for Evidence-Based Medicine (Table 2).⁴⁴ Following this system, RCTs at low risk of bias were graded as level 2 evidence, non-RCTs at low risk of bias were considered level 3 evidence, and case series were considered level 4 evidence. The level of evidence of individual studies could be downgraded based on study imprecision, risk of bias, and study indirectness or because of small effect sizes. The level of evidence of individual studies could be upgraded based on large effect size.

RESULTS

Study Selection

We included 8 trials, including 4 recent trials that were not included in our 2017 systematic review.^{16,23,41,48} Figure 1 shows the study flow diagram. We identified 4 unpublished trials in trial registries.^{15,39,40,47} We made attempts to contact the authors of these trials by email. The authors of 1 trial replied and reported that their trial was under review.⁹ The authors of the other 3 trials did not provide information about the status of their trials.

Study Characteristics

Of the 8 studies included in this review, 1 was an RCT,⁴⁸ 3 were non-RCTs,^{14,17,18} and 4 were case series.^{12,22,34,41} These studies focused on stem cell therapy for tendon disorders of the lateral elbow²² and rotator cuff^{12,14,17,18} and the Achilles^{41,48} and patellar tendon,³⁴ including a total of 289 patients (135 males, 154 females; age range, 14-74 years). The study populations consisted of athletes and nonathletes. Study characteristics are summarized in Table 3.

Of the 8 studies, 3 studies evaluated the efficacy of allogenic adipose-derived stem cells (allo-ASCs).^{18,22,48} The efficacy of bone marrow mononuclear stem cells (BMMCs) was investigated in 2 studies,^{12,34} the efficacy of bone marrow aspirate concentration (BMACs) in 2 studies,^{17,41} of

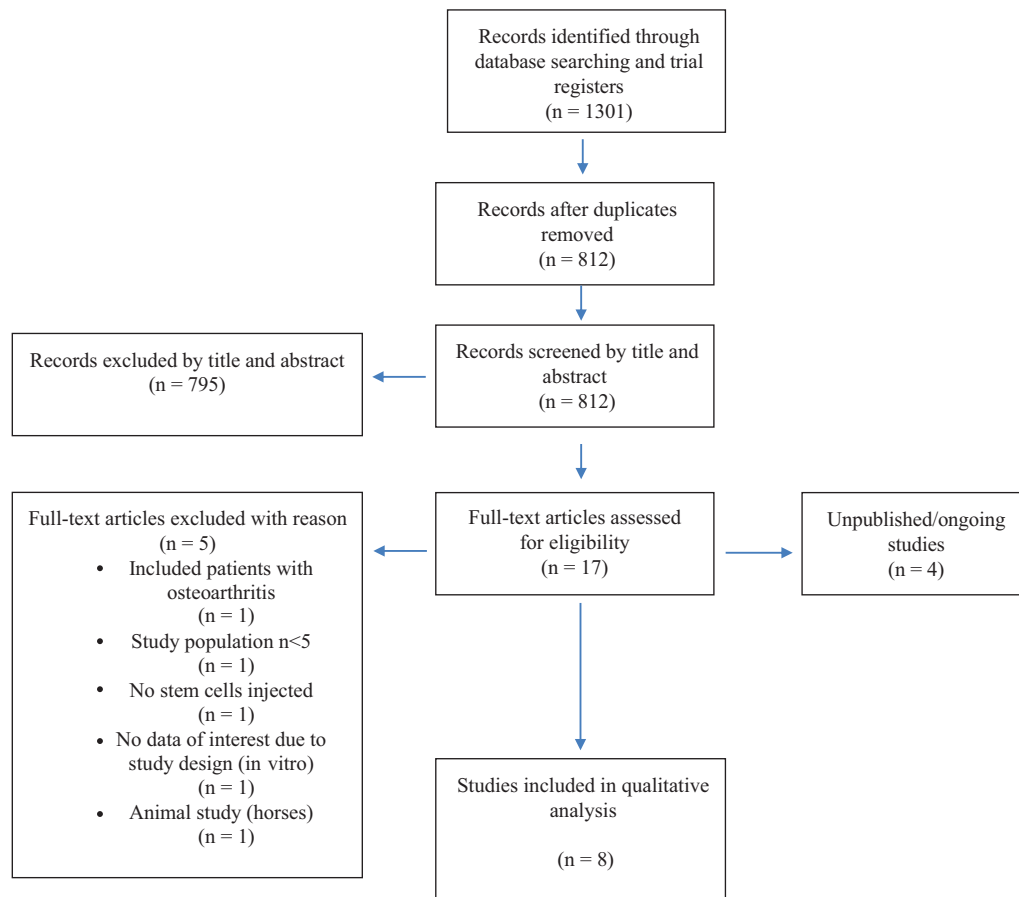


Figure 1. Study flowchart based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

which 1 study combined BMACs with platelet-rich plasma (PRP).¹⁷ Efficacy of stem cell therapy was measured using PROMs in 7 of the 8 studies.^{12,17,18,22,34,41,48} In 1 study,¹⁴ the investigators assessed efficacy of treatment using MRI and ultrasonography. In 7 of the 8 studies,^{12,14,17,18,22,34,48} investigators evaluated tendon healing using MRI or ultrasonography. Due to study heterogeneity, descriptive data synthesis was performed.

Risk of Bias in Individual Trial Outcomes

Domain-based risk of bias assessments for the non-RCTs and RCTs are presented in Table 4. The RCTs examined the efficacy of stromal vascular fraction (allo-ASC) versus PRP injection in patients with tendinopathy based on PROMs, MRI, and ultrasonography.⁴⁸ High risk of bias was found for the overall judgment. The non-RCTs were found at high or moderate risk of bias for all PROMs. Ultrasound outcomes were found at moderate risk of bias for the overall judgment. Only MRI outcomes were found at low risk of bias in 1 non-RCT that investigated the efficacy of allo-ASC injection versus arthroscopic rotator cuff repair.¹⁸ Quality of case series varied; they received between 2 and 5 stars out of 6 stars in total. See Appendices 2 and 3 for all risk of bias judgements.

Efficacy of Stem Cell Injections for Tendon Disorders

Achilles Tendon Disorders

Achilles Tendinopathy. Usuelli et al⁴⁸ examined the efficacy of allo-ASC injection versus PRP injection in patients with noninsertional Achilles tendinopathy with a total follow-up of 6 months. At 15 days after treatment, the mean American Orthopaedic Foot and Ankle Society (AOFAS) score was significantly higher in the allo-ASC group than in the PRP group (80 vs 67, respectively; $P < .05$). The mean visual analog scale (VAS) score was significantly lower in the allo-ASC group than the PRP group at 15 days after treatment (2.5 vs 4.5, respectively; $P < .05$). There was no difference between the groups in the Victorian Institute of Sports Assessment–Achilles questionnaire (VISA-A) score at 15 days of follow-up ($P > .05$). At a follow-up of 30 days, the mean VAS pain score was 2.0 in the allo-ASC group and 4.0 in the PRP group ($P < .05$). The mean VISA-A score was 60 in the allo-ASC group and 47 in the PRP group ($P < .05$). The AOFAS score was 80 in the allo-ASC group and 70 in the PRP group ($P > .05$). After 60 days of follow-up, there were no differences in PROMs between patients treated with allo-ASC and PRP injection.

Achilles Tendon Tears. Stein et al⁴¹ examined the outcomes of primary Achilles tendon rupture repair with BMAC

TABLE 3
Study Characteristics^a

Lead Author (Year)	Study Design	Sample Size	Injury Type	Demographics ^b	Treatment	Outcome Measures	Follow-up	Level of Evidence
Usuell ⁴⁸ (2018)	RCT	Group 1: n = 23 Group 2: n = 21	Achilles tendinopathy	Group 1 (C) • Age, 46.6 ± 6.2 (18-55) • Females, 15 (65%) Group 2 (I) • Age, 47.3 ± 3.8 (18-55) • Females, 7 (33%)	Group 1: PRP Group 2: allo-ASC	• VAS pain score • VISA-A score • AOFAS score • SF-36 score • MRI evaluation • Ultrasound evaluation	6 mo	3
Stein ⁴¹ (2015)	Case series	N = 27	Achilles tendon rupture	• Age, 38.3 ± 9.6 • Females, 6 (22%)	BMAC	• Mean difference in calf circumference (cm) • Time to walking without boot (mo) • Returned to sport or not • ATRS	24 mo	4
Kim ¹⁸ (2017)	Non-RCT	Group 1: n = 35 Group 2: n = 35	Rotator cuff tear	Group 1 (C) • Age, 57.6 ± 2.9 (45-70) • Females, 22 (63%) Group 2 (I) • Age, 59.2 ± 3.4 (40-76) • Females, 20 (57%)	Group 1: arthroscopic rotator cuff repair Group 2: allo-ASC	• VAS pain score • Constant score • UCLA score • ROM • MRI: structural outcomes	24 mo	3
Hernigou ¹⁴ (2014)	Non-RCT	Group 1: n = 45 Group 2: n = 45	Rotator cuff tear	Group 1 (C) • Age, 61 (49-71) • Females, 25 (62%) Group 2 (I) ^c	Group 1: surgical repair with an arthroscopic protocol Group 2: MSC	• MRI for number of stem cells correlated for cuff healing • MRI for number of retears • Ultrasonography for evaluation of healing surface	10 y	3
Kim ¹⁷ (2018)	Non-RCT	Group 1: n = 12 Group 2: n = 12	Partial rotator cuff tear	Group 1 (C) • Age, 59.6 ± 7.2 • Females, 4 (33%) Group 2 (I) • Age, 54.9 ± 7.6 • Females, 7 (58%)	Group 1: rotator cuff strengthening exercise Group 2: BMAC-PRP	• VAS pain score • MMT score • ASES score • Medication frequency change • Ultrasonography for tear size evaluation	3 mo	3
Ellera Gomes ¹² (2012)	Case series	N = 14	Rotator cuff tear	• Age, 59.2 • Females, 9 (64%)	BMMC	• UCLA score • MRI for tendon healing	12 mo	4
Pascual-Garrido ³⁴ (2012)	Case series	N = 8	Patellar tendinopathy	• Age, 24 (14-35) • Females, 4 (50%)	BMMC	• Lysholm score • Tegner score • IKDC score • KOOS • SF-12 score • Ultrasonography for tendon healing	24 mo	4
Lee ²² (2015)	Case series	N = 12	Lateral epicondylar tendinopathy	• Age, 51.8 ± 9.5 • Females, 6 (58%)	Allo-ASC	• VAS score • MEPI score • Ultrasonography for structural healing	52 wk	4

^aAOFAS, American Orthopaedic Foot and Ankle Society; ASC, adipose-derived stem cell; ASES, American Shoulder and Elbow Surgeons; ATRS, Achilles Tendon Rupture Score; BMAC, bone marrow aspirate concentrate; BMMC, bone marrow mononuclear cells; C, comparison group; I, intervention group; IKDC, International Knee Documentation Committee; KOOS, Knee injury and Osteoarthritis Outcome Score; MEPI, Mayo Elbow Performance Index; MMT, manual muscle test; MRI, magnetic resonance imaging; MSC, bone marrow-derived mesenchymal stem cells; PRP, platelet-rich plasma; RCT, randomized controlled trial; ROM, range of movement; SF-12, 12-Item Short Form Health Survey (mental and physical); SF-36, 36-Item Short Form Health Survey questionnaire; UCLA, University of California, Los Angeles; VAS, visual analog scale; VISA-A, Victorian Institute of Sport Assessment–Achilles questionnaire.

^bAge is expressed in years as mean or mean ± SD, with range (if available) in parentheses. Data for female participants are expressed as n (%).

^cAge and sex were not clearly described; the authors only mentioned there was no significance difference with comparison group.

TABLE 4
Risk of Bias Judgment for Randomized and Nonrandomized Controlled Trials^a

Randomized Controlled Trial			
Usuelli et al ⁴⁸ (2018)			
Outcome	<i>Primary:</i> VAS, VISA-A, AOFAS, SF-36 <i>Secondary:</i> MRI, US		
Intervention vs control groups	<i>Intervention:</i> allo-ASC injection <i>Control:</i> PRP injection		
Risk of bias			
Bias arising from the randomization process	Some concerns		
Bias due to deviations from intended interventions	High risk		
Bias due to missing outcome data	Low risk		
Bias in measurement of the outcome	<i>Intervention:</i> some concerns <i>Control:</i> low risk		
Bias in selection of the reported result	Some concerns		
Overall risk of bias judgment	High risk		
Nonrandomized Controlled Trials			
	Kim et al ¹⁷ (2018)	Kim et al ¹⁸ (2017)	Hernigou et al ¹⁴ (2014)
Outcome	<i>Primary:</i> VAS, MMT, ASES <i>Secondary:</i> US	<i>Primary:</i> VAS, ROM, UCLA, Constant score <i>Secondary:</i> MRI	<i>Primary:</i> PROMs (not measured) <i>Secondary:</i> MRI, US
Intervention vs control groups	<i>Intervention:</i> BMAC-PRP injection <i>Control:</i> Exercise	<i>Intervention:</i> allo-ASC with arthroscopy <i>Control:</i> Arthroscopy	<i>Intervention:</i> MSC injection with arthroscopy <i>Control:</i> Arthroscopy
Risk of bias			
Bias due to confounding	VAS, MMT, ASES: moderate risk US: low risk	VAS, ROM, UCLA, Constant: moderate risk MRI: low risk	Low risk
Bias in selection of participants into the study	Low risk	Moderate risk	Moderate risk
Bias in classification of interventions	Low risk	Low risk	Moderate risk
Bias due to deviations from intended interventions	Low risk	Low risk	Low risk
Bias due to missing data	Low risk	Low risk	Low risk
Bias in measurement outcomes	VAS, MMT, ASES: serious risk US: moderate risk	VAS, ROM, UCLA, Constant: moderate risk MRI: low risk	Moderate risk
Bias in selection of the reported result	Moderate risk	Low risk	Low risk
Overall risk of bias judgment	VAS, MMT, ASES: high risk US: moderate risk	VAS, ROM, UCLA: moderate risk MRI: low risk	Moderate risk

^aRisk of bias judgments apply to all study outcomes listed unless otherwise specified. AOFAS, American Orthopaedic Foot and Ankle Society; ASC, adipose-derived stem cell; ASES, American Shoulder and Elbow Surgeons; BMAC, bone marrow mononuclear stem cell; MMT, manual muscle test; MRI, magnetic resonance imaging; MSC, bone marrow-derived mesenchymal stem cells; PROM, patient-reported outcome measure; PRP, platelet-rich plasma; ROM, range of movement; SF-36, 36-Item Short Form Health Survey questionnaire; UCLA, University of California, Los Angeles; US, ultrasonography; VAS, visual analog scale; VISA-A, Victorian Institute of Sports Assessment–Achilles questionnaire.

augmentation. In that study, 27 patients underwent open repair procedures augmented with BMAC injection. All patients could walk without a boot at 1.8 ± 0.7 months and participated in light activity at 3.4 ± 1.8 months, and 25 of 27 patients (92%) returned to sport at 5.9 ± 1.8 months. At a mean follow-up of 29.7 ± 6.1 months, no reruptures of Achilles tendons were reported. The mean Achilles Tendon Rupture Score at final follow-up was 91 points (range, 72–100 points).

Level of Evidence. There is level 3 evidence for a superior effect of allo-ASC injections for Achilles tendinopathy compared with PRP injections on PROMs at 15 and 30 days after injection, but no differences were observed at 60 days of follow-up. There is level 4 evidence for improved PROMs and absence of reruptures 2.5 years after open Achilles tendon repair with BMAC augmentation.

Rotator Cuff Tendon Tears

We identified 3 non-RCTs that examined the efficacy of stem cell injections in rotator cuff tendon tears. The first trial determined the efficacy of allo-ASC injection during arthroscopic rotator cuff repair, comparing the double-row suture bridge technique with injection versus the double-row suture bridge technique alone in patients with rotator cuff tears.¹⁸ At 21 months of follow-up, the mean Constant score was 78.3 ± 14.9 in the intervention group and 80.1 ± 13.2 in the control group ($P = .634$). The mean University of California, Los Angeles (UCLA) Shoulder Rating Scale score was 29.8 ± 5.1 in the intervention group and 30.5 ± 4.8 in the control group ($P = .302$). The mean VAS pain score at rest was 0.4 ± 0.6 for the allo-ASC group and 0.3 ± 0.5 for the control group ($P = .776$). The VAS pain score during motion was 2.4 ± 1.1 in the allo-ASC group and 2.1 ± 0.9 in the control group ($P = .256$). At minimum of 12 months after intervention, a retear rate of 28.5% was found with MRI in the control group versus 14.3% in the stem cell injection group ($P < .001$). Complete healing of the tendon, as measured with MRI, was observed in 85.7% of patients in the intervention group versus 71.4% of patients in the control group.

The second trial evaluated the efficacy of bone marrow-derived mesenchymal stem cells (MSCs) injection as an adjunct to single-row rotator cuff arthroscopy in comparison with single-row rotator cuff arthroscopy alone in patients diagnosed with rotator cuff tears.¹⁴ The total follow-up was 10 years. In the BMAC group, significantly fewer retears were reported after 10 years of follow-up as measured by MRI and ultrasonography (13% vs 56%, respectively; $P < .05$).

The third trial studied the efficacy of an injection with BMAC-PRP versus exercise therapy in patients diagnosed with a rotator cuff tear with a total follow-up of 3 months.¹⁷ At 3 weeks postoperatively, mean VAS pain scores were 2.3 ± 0.8 in the BMAC-PRP group and 3.6 ± 2.3 in the control group ($P = .147$). The mean American Shoulder and Elbow Surgeons (ASES) score was 74.1 ± 8.4 in the BMAC-PRP group versus 62.2 ± 12.2 in the control group at final follow-up ($P = .011$). The mean VAS pain score was 1.9 ± 0.7 in the intervention group and 3.7 ± 1.8 in the control group at final follow-up ($P = .039$).

In addition, 1 case series examined the efficacy of BMMC augmentation in patients undergoing surgery for complete rotator cuff tears. In that series, 14 consecutive patients were treated with transosseous stitches through mini-open incision and subsequent BMMC injection obtained from the iliac crest.¹² The minimum follow-up was 12 months. The UCLA score was used as main outcome; this score increased from 12 ± 3.0 to 31 ± 3.2 , and no statistical analysis was performed in this study.

Level of Evidence. There is level 3 evidence for a superior effect of allo-ASC injection augmentation for rotator cuff tears compared with arthroscopic double-row suture bridge technique alone on tendon healing and retears as measured by MRI. However, no significant differences have been observed between surgical

rotator cuff repair with and without allo-ASC augmentation on PROMs (level 3). There is level 3 evidence for a superior effect of arthroscopic single-row rotator cuff repair with BMMC augmentation in comparison with arthroscopic single-row rotator cuff repair for retears as measured by MRI and ultrasonography. There is level 4 evidence for a superior effect of BMAC-PRP on rotator cuff tears compared with exercise therapy for the ASES score and VAS pain score at 3 months after injection. Table 2 provides more information about the level of evidence.

Patellar Tendinopathy

One case series studied the efficacy of BMMC injection for patients with chronic patellar tendinopathy (lasting at least 6 months).³⁴ The follow-up time of the patients was at least 24 months. The following PROMs increased significantly over time: Tegner Activity Scale score ($P = .006$), International Knee Documentation Committee score ($P = .047$), and Knee injury and Osteoarthritis Outcome Score (KOOS) for the subdomains Activities of Daily Living ($P = .008$) and Function during Sports/Recreation ($P = .0078$). No statistical improvement was observed for the Lysholm score ($P = .1043$), KOOS for Pain ($P = .2399$), KOOS for Quality of Life ($P = .0825$), and 12-item Short Form Health Survey questionnaire for mental and physical domains ($P = .5589$ and $P = .438$, respectively). Tendon structures, as assessed with ultrasonography, did not change between baseline and follow-up.

Level of Evidence. There is level 4 evidence for improved PROMs after BMMC injections for patients with chronic patellar tendinopathy at least for 24 months of follow-up.

Lateral Elbow Tendinopathy

Lee et al²² studied the efficacy of an allo-ASC injection in a case series of patients with lateral elbow tendinopathy. The total follow-up period was 52 weeks. The Mayo Elbow Performance Index was 64.0 ± 13.5 at baseline and 87.1 ± 11.6 , 89.2 ± 6.8 , 92.1 ± 6.1 , and 90.6 ± 5.8 after 6, 12, 23, and 52 weeks, respectively. Compared with baseline, these were significant improvements at all follow-up points ($P = .002$). The VAS pain score during motion was 66.8 ± 14.6 at baseline, 42.1 ± 23.2 at 6 weeks after injection ($P = .004$), 31.1 ± 20.6 at 12 weeks ($P = .002$), 15.3 ± 13.7 at 26 weeks ($P = .002$), and 14.8 ± 13.1 at final follow-up at 52 weeks ($P = .002$). The VAS scores after 26 and 52 weeks were also significantly lower than those at 6 weeks ($P = .006$ and $P = .008$, respectively) and at 12 weeks after injection ($P = .013$ and $P = .034$, respectively). For ultrasound evaluation of the tendon structure, the largest average defect area was $6.46 \pm 3.37 \text{ mm}^2$ at baseline, $2.34 \pm 1.42 \text{ mm}^2$ after 26 weeks, and $3.06 \pm 1.32 \text{ mm}^2$ ($P = .003$) after 52 weeks for the longitudinal axis. For the transverse axis, the average largest defect area was $8.14 \pm 3.99 \text{ mm}^2$ at baseline, $3.36 \pm 1.94 \text{ mm}^2$ after 26 weeks ($P = .002$), and $4.31 \pm 2.10 \text{ mm}^2$ after 52 weeks ($P = .015$).

Level of Evidence. There is level 4 evidence for improved PROMs and ultrasound evaluation of the tendon healing after allo-ASC injection at all follow-up periods.

DISCUSSION

The purpose of this systematic review was to evaluate the evidence of stem cell therapy in the treatment of tendon disorders. To date, the efficacy of stem cell therapy has been examined in 8 studies of Achilles tendon, rotator cuff tendon, and patellar tendon disorders and lateral elbow tendinopathy.^{12,14,17,18,22,34,41,48} We found level 3 evidence for the superior effect of stem cell therapy compared with treatment without stem cells. This update shows that there is still a moderate to high risk of bias for studies evaluating stem cell therapy for tendon disorders.

How Does the Evidence for Stem Cell Therapy Compare With the Evidence for Other Treatments for Tendon Disorders?

Level 3 evidence for the use of stem cell therapy in tendon disorders implies that we cannot yet recommend its use in clinical practice. Except in the trial by Kim et al,¹⁸ stem cell therapy has not been compared with commonly used therapies such as exercise therapy or extracorporeal shockwave therapy (ESWT). Moreover, the duration of follow-up was relatively short in the trial by Kim et al.¹⁷ This makes it challenging to judge whether stem cell therapy should be preferred over conventional treatments in the management of tendon disorders.

Compared with stem cell therapy, other therapies have a larger body of evidence underpinning their efficacy, although their evidence is also moderate to low. A recent systematic review on the treatment of Achilles tendinopathy concluded that eccentric exercises may be better than wait-and-see and traditional physiotherapy.²⁹ The evidence for this was, respectively, very low and low. Another commonly applied intervention for Achilles tendinopathy is ESWT. The recent systematic review by Korakakis et al¹⁹ reported that low-level evidence is available to show ESWT comparable with eccentric training and superior to wait-and-see. Those investigators also concluded that moderate evidence exists for ESWT being equal to sham ESWT for individuals with patellar tendinopathy. A systematic review published in 2016 described the results of eccentric training for tendinopathy of the rotator cuff and lateral elbow tendinopathy.³² It concluded that eccentric training may be more effective in treating an upper extremity condition than any other nonoperative form of therapy. However, this systematic review also lacked strong evidence.

All of the aforementioned systematic reviews suggested that the evidence for tendon disorder treatment is at best moderate to low. Yet, we do not recommend stem cell therapy as an alternative to these therapies. This is because of the invasive character of stem cells and their potential side effects. In the sections below, we explain the working mechanism and potential adverse effects of stem cells that merit

further consideration before the limited evidence is put into practice.

Theoretical Evidence for the Efficacy of Stem Cell Therapy

Stem cells may be derived from many different tissues. In the studies included in this review, cells were derived from either bone marrow (BMACs, BMMCs, MSCs) or adipose tissue (allo-ASC). In most studies, plain unsorted cells were administered with an unknown number of stem cells. Only 1 study described a correlation between the actual number of stem cells (CD34+) and treatment outcome.¹⁴

There are 2 theories on the efficacy of stem cell treatments for tendon disorders. It is thought that tendon healing is supported by paracrine effects of injected stem cells, secreting various growth factors and cytokines that may mend injured tendons.^{2,6,8,24,26,27} Theoretically, tendon healing may also be improved by stem cell differentiation into tenocytes. In vitro studies have shown stem cell therapies to provide tendon regeneration rather than repair of the tendon tissue.⁴⁹ This regeneration includes replacement of the damaged tendon fibers with identical “new” tissue.⁴⁹ Regeneration occurs in all embryos, hardly ever occurs in neonates, and is never observed in adults.⁴⁶ In contrast to regeneration, tendon repair is a more rapid process encompassing the inflammatory cell cascade, the deposition of matrix, and remodeling.³⁰ Tendon tissue regeneration is an alternative for replacement of large damaged tissue based on a combination of embryonic or adult stem cells.³⁶

Stem Cells and Their Potential to Harm

Stem cells may cause serious harm despite their potential to heal. Recently, the Food and Drug Administration warned of serious potential risks to patients from stem cell therapies administered for uses other than hematopoietic or immunologic reconstitution.³⁵ Numerous infections were reported after receipt of bacterially contaminated umbilical cord blood–derived stem cell products. Autologous hematopoietic stem cells injected into the kidneys of a patient with renal failure were associated with the development of tumors that eventually led to nephrectomy.⁴⁵ In another instance, autologous stem cells derived from adipose tissue and injected intravitreally into the eyes of people with macular degeneration were associated with worsening vision in 3 people, 2 of whom became blind.²¹ A patient who underwent intrathecal mesenchymal, embryonic, and fetal neural stem cell infusions for the treatment of an ischemic stroke developed a glioma that was derived from the injected stem cells.⁷ In cases of stem cell administration for tendon healing, adverse effects have not been reported. As shown in bone marrow–derived stem cells and ASCs, there is risk of ectopic bone and tumor formation under special circumstances.²⁵

Given the paucity of studies following patients with tendon disorders after a stem cell injection for prolonged

periods of time, the extent to which stem cell therapy is associated with serious harm is presently unknown.

Future Directions

Due to considerable bias and lack of high-level evidence supporting the use of stem cell therapy, we are currently not able to recommend stem cell therapy for patients with tendon disorders. Many gaps in our knowledge remain with regard to safety, indications, dosage, and concentration of the stem cells and harvesting methods.^{10,13,14,17} There is a need for large, methodologically sound RCTs that are reported according to the CONSORT (Consolidated Standards of Reporting Trials) statement.³⁸ Considering the available evidence, RCTs should compare stem cell therapy to evidence-based treatments like ESWT and exercise therapy.^{11,29} Another issue that warrants attention is the standardized evaluation and reporting of potential harmful effects of stem cell therapies. Follow-up should be at least 5 years to monitor possible severe harmful effects.

Strengths and Limitations

We used a sensitive search strategy in 6 different databases and assessed risk of bias based on the latest standards. We also included 1 trial investigating the combination of stem cell therapy with PRP injection.¹⁷ We believe this combination of PRP with stem cells is relevant in the evaluation of the efficacy of stem cell therapy for tendon disorders and, therefore, is a strength of this review. A limitation is the absence of information about ongoing studies, despite our best efforts to obtain such information.

CONCLUSION

Despite promising results of various individual studies on the use of stem cells in the treatment of various tendon disorders, there is currently no high-level evidence that justifies an evidence-based recommendation of stem cell therapy. Stem cell injections should not be used in clinical practice given the lack of knowledge about potentially serious adverse effects.

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SUPPLEMENTAL MATERIAL

Appendices 1-5 for this article are available at <https://journals.sagepub.com/doi/suppl/10.1177/2325967120915857>

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